Message

From: Pratt, Margaret [pratt.margaret@epa.gov]
Sent: 5/8/2014 8:43:30 PM
To: McClure, Peter [mcclure@srcinc.com]; Hogan, Karen [Hogan.Karen@epa.gov]
CC: Chiu, Weihsueh [Chiu.Weihsueh@epa.gov]; Flowers, Lynn [Flowers.Lynn@epa.gov]; Rice, Glenn [rice.glenn@epa.gov]; Carlson-Lynch, Heather [hclynch@srcinc.com]; Melia, Julie [jmelia@srcinc.com]
Subject: RE: BPA#: EP-BPA-11-C-0018; Contract No. GS-00F-0019L; TO#: EP-B14C-00008: Response to question about incidences from Hoffman and Wynder, 1966 (PAHs16-25)

Hi Peter,

Thanks for the information!

I will ask Karen today if she has any thoughts on this as she will not be able to join us tomorrow.

Danke!
Margaret

From: McClure, Peter [mailto:mcclure@srcinc.com]
Sent: Thursday, May 08, 2014 4:38 PM
To: Pratt, Margaret; Hogan, Karen
Cc: Chiu, Weihsueh; Flowers, Lynn; Rice, Glenn; Carlson-Lynch, Heather; Melia, Julie
Subject: FW: BPA#: EP-BPA-11-C-0018; Contract No. GS-00F-0019L; TO#: EP-B14C-00008: Response to question about incidences from Hoffman and Wynder, 1966 (PAHs16-25)

Hi Margaret,
You ask an interesting question, that led Dave Wohlers (he speaks and reads German) and I to look at the Hoffman and Wynder 1966 report again.

Here is a rough translation of the process by which tumors were detected on mice from page 141 of the report.

Appearance of a 1- mm lesion was counted as a papilloma (and a tumor), if there was no regression within 3 weeks of first detection.
A lesion was suspected as an epithelioma if lateral growth from the papilloma was found macroscopically. The time of detection of the lateral growth was considered as the initiation (auftreten) of the epithelioma.
Four to five weeks after detection of epithelioma, individual mice were sacrificed for histological confirmation of carcinoma.
To compare relative activities of test compounds, middle latency periods were calculated (time at which 50% of tumors were observed).

In the Results and Discussion section, the authors used middle latency periods to compare relative activities of the test compounds. Dave and I could find no discussion of causes of death in this study report.

So, the only information about mortality comes from the columns recording the number of surviving animals in each monthly period for each test compound in Table 1. From examining that middle column for DBaiP, we infer that some deaths occurred that were not tumor-related sacrifice deaths, but it is not possible to quantify the number from Table 1 data, except for the monthly periods before epitheliomas were first detected.

In the past, incidences (used to calculate RPFs) were constructed with the total number of animals detected with papillomas within the 15-month period in the numerator and the number of surviving animals in the month preceding the first detection of papilloma in the denominator. Tomorrow, can we include discussion of options for other ways of constructing incidences from Table 1 of Hoffman and Wynder 1966?

Thanks,
Peter

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From: Pratt, Margaret [mailto:pratt.margaret@epa.gov]
Sent: Wednesday, May 07, 2014 1:46 PM
To: McClure, Peter; Hogan, Karen
Cc: Chiu, Weihsueh; Flowers, Lynn; Rice, Glenn; Melia, Julie; Carlson-Lynch, Heather
Subject: RE: BPA#: EP-BPA-11-C-0018; Contract No. GS-00F-0019L; TO#: EP-B14C-00008: PAHs 16-25

Hi Peter,

For clarification, I've translated some of the methodology using Google, but would like to check your understanding. Specifically for BaP (labeled as "X"), the table shows "0" surviving animals at 7 months, but from the translation it seems they were sacrificing the animals 4-5 weeks after appearance of the first tumor. Is there any information about mortality in the absence of tumors, or were all recorded deaths due to tumor-related sacrifice? Just wondering about the number that should be used in the denominator.

Secondly, in showing the month 15 data, is that to demonstrate that BrstPP treatment will ultimately lead to tumor formation, even though we cannot calculate an RPF because the dose of BaP was too potent?

Thanks!
Margaret

From: McClure, Peter [mailto:mcclure@srcinc.com]
Sent: Wednesday, May 07, 2014 9:11 AM
To: Pratt, Margaret; Hogan, Karen
Cc: Chiu, Weihsueh; Flowers, Lynn; Rice, Glenn; Melia, Julie; Carlson-Lynch, Heather
Subject: RE: BPA#: EP-BPA-11-C-0018; Contract No. GS-00F-0019L; TO#: EP-B14C-00008: PAHs 16-25

Margaret, Karen, et al.:

Thank you for your responses. The following are SRC actions taken in response to your responses.

1. For PAHs 16-20, we will:

a. Borrow from Wood et al. 1980 for BcPH data from Levin et al. 1980

2. For PAHs 21-25,

a. we provide the following table for BrstPP tumor incidence data from Hoffman and Wynder (1966). We think the incidence data for the 7-month sacrifice for both BrstPP and Bap are suitably low for modeling, so we have not extracted the 6-month data. Please let us know if this presentation of the incidence data is clear to you.

Species, strain, sex and purity, vehicle	Exposure protocol and follow-up	Tumor type(s) observed	Tumor response – Incidence [multiplicity][a]					BMD_{10} (µg)	RPF	Reference and comments
			Control[b]	BrstPP		BaP				
				Dose (µg)	Response	Dose (µg)	Response			
Dermal complete studies										
Mouse Ha/ICR/Mil Swiss Female Purity not reported Dioxane	3 times/wk for 52 wks Follow-up up to 65 wks Dose units: %; µg could not be calculated from the data presented in the report.	Skin papillomas at month 7	0/20	0.05% 0.1%	0/19 3/20	0.05% 0.1%	16/20* 19/20*	BrstPP = BaP =		Hoffman and Wynder, 1966 Doses reported as %; not enough information to calculate µg
		Skin papillomas at month 15	0/20	0.05% 0.1%	16/19* 16/20*	0.05% 0.1%	17/20* 19/20*			

Peter

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From: Pratt, Margaret [mailto:pratt.margaret@epa.gov]
Sent: Tuesday, May 06, 2014 6:39 PM
To: McClure, Peter; Hogan, Karen
Cc: Chiu, Weihsueh; Flowers, Lynn; Rice, Glenn; Melia, Julie; Carlson-Lynch, Heather
Subject: RE: BPA#: EP-BPA-11-C-0018; Contract No. GS-00F-0019L; TO#: EP-B14C-00008: PROPOSED WORK PAHS #16-20 AND 21-25

Hi Peter,

Here are responses to the requests for clarification. First, for PAHs 16-20:

1. Bayesian BMDs—
- BeP, Slaga et al., 1980a,b—Yes, have added to list for Bayesian modeling.
- BeP, Deutsch-Wenzel et al., 1983—No, it's non-physiological; there are physiological route studies that will be used.
- BghiPery, Hoffman and Wynder, 1966—Probably not. If so, one would be needed for VanDuuren and Goldschmidt as well.

2. Determinations whether to borrow BaP data from studies conducted 1 year earlier or later:
- BcPH, Levin et al., 1980—Go ahead and borrow from Wood et al. 1980.

- BjFA, Weyand et al., 1992; use Lavoie et al., 1993c or Rice et al., 1987?—Still postponing for an overall resolution for studies from this group.

Here are responses for PAHs 21-25:

- Determination of whether or not SRC should do any further work with data for BkFA from Habs et al. (1980)—We'll consider Bayesian modeling for this. It's close to RPF=0
- Bayesian BMD for BrstPP in Hoffman and Wynder 1966, so 7-month data can be used per EPA instructions—Yes, we'll add it to the list for Bayesian modeling. Please provide the incidence data, not clear now how to read the tables. If the BaP incidence data are too high, also please provide the incidence for both PAHs at Month 6. Maybe the timecourses don't match up well enough in either case.
- Determination of whether Bayesian BMD will be provided for male mice in i.p. studies of BkFA (LaVoie et al. 1987) and CH (Wislocki et al. 1986)—No, we'll rely on the physiological studies.
- Determination of whether or not to borrow BaP data from a study 1 year later, for studies of BkF (Amin et al. 1985b), BrstPP (Hecht et al. 1981), and CH (Wood et al., 1979; available BaP data are from study with different protocol; see table)—Can't say yet for Amin or Hecht (LaVoie lab studies); different TPA doses makes Wood et al. 1980 an unsuitable source of BaP data.
- Determination of whether or not to model non-monotonic data on CPcdP from Cavalieri et al. (1981a,b) dermal initiation study—No, the concurrent BaP data were not suitable.

Please let me know if you have questions or comments.

Thanks!
Margaret

From: McClure, Peter [mailto:mcclure@srcinc.com]
Sent: Friday, May 02, 2014 4:31 PM
To: Hogan, Karen; Pratt, Margaret
Cc: Chiu, Weihsueh; Flowers, Lynn; Rice, Glenn; Melia, Julie; Carlson-Lynch, Heather
Subject: RE: BPA#: EP-BPA-11-C-0018; Contract No. GS-00F-0019L; TO#: EP-B14C-00008: PROPOSED WORK PAHS #16-20 AND 21-25

Margaret, Karen et al.
Thanks for your comments. Attached are files with summaries of proposed work for PAHs #16-20 AND 21-25. More to come.
We look forward to your responses.
Peter

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From: Hogan, Karen [mailto:Hogan.Karen@epa.gov]
Sent: Friday, May 02, 2014 11:45 AM
To: Pratt, Margaret; McClure, Peter; Melia, Julie; Carlson-Lynch, Heather
Cc: Chiu, Weihsueh; Flowers, Lynn; Rice, Glenn

Subject: RE: BPA#: EP-BPA-11-C-0018; Contract No. GS-00F-0019L; TO#: EP-B14C-00008: PROPOSED WORK PAHS #1-5

Dear all,

Ex. 5 Deliberative Process (DP)

Thanks,
Karen